ON THE PHYSIOLOGICAL ACTION OF THE CALABAR BEAN (*Physostigma venenosum*, Balf.).

By THOMAS R. FRASER, M.D. F.R.S.E. Assistant to the Professor of Materia Medica in the University of Edinburgh.

THE peculiar actions of Calabar Bean on the pupil and on vision have been investigated by nearly all the leading ophthalmologists of Europe and of America, but the general physiology of this substance has occupied the attention of comparatively few observers. The results obtained by the latter have been discordant, and, therefore, many of their conclusions are of necessity erroneous. This investigation was undertaken for the purpose of establishing and supporting the opinions I published on this subject in 1863. The leading results obtained at that time were that Calabar Bean causes death by either asphyxia or syncope; that the former is due to an effect on the spinal cord and on the respiratory centres; and that the symptoms resemble those of syncope or asphyxia according to the quantity of poison administered and to its rate of absorption[1].

The actions on the pupil and on vision will be merely alluded to, as this portion of the subject has not been completed. Enough has, however, been done to convince me of the insufficiency of the views hitherto advanced and to suggest the advisability of extending my observations.

To Professor Harley, of London, we are indebted for several very able papers on this subject. The principal conclusions at which he arrived were, that Calabar Bean paralyses the motor nerves and so causes death by asphyxia, and that, while it may weaken the heart's power, it neither stops the circulation nor arrests the heart's action: in fact, that the mechanism of death by Calabar Bean is very much the same as that by either curare or conia[2]. The result of my investigations obliges me to express my non-concurrence with Dr Harley's conclusions. Calabar Bean causes death by asphyxia; but the most careful examination has failed in shewing me that this asphyxia is due to a paralysis of the motor nerves. In more than one hundred and twenty experiments in which I tested the condition of these nerves immediately after death, stimulation, whether galvanic or by means of dilute acids, invariably gave evidence of their continued activity; and I have never found that the motor conductivity has been destroyed until a considerable interval has elapsed since the arrest of the respiratory movements. Dr Harley alludes to an experiment on a rabbit, in which he tested the condition of the motor nerves, but he does not, unfortunately, mention how long after death his examination was made[3]. I have found that the interval during which they remain active varies greatly in different animals, and in the same animal according to the dose of poison administered. In the rabbit, motor conductivity may be retained for periods ranging from four to thirty-one minutes, and it may be lost within eight minutes after the autopsy was commenced, which was never done, in these experiments, until a few minutes after respiration had ceased. A distinct but short period has always occurred in dogs and rabbits, and a much longer one in frogs, in which it was unimpaired. I am inclined to account for this misstatement on the part of so acute an observer, by supposing that the examination of the motor nerves had not been made *very soon* after death.

We must, therefore, look to other causes for an explanation of the asphyxia which is sometimes produced. An examination of the diastaltic

[1] On the Characters, Actions and Therapeutic Uses of the Ordeal Bean of Calabar, *Edin. Med. Journal*, 1863; and Pamphlet. Graduation Thesis, 1862.

[2] *Journal de l'Anatomie et de la Physiologie*, 1864, p. 141 et seq.

[3] *Op. cit.* p. 151.

function of the spinal cord confirms, in the most satisfactory manner, the opinion which I originally expressed, that this symptom is caused by an effect on the spinal cord, of such a nature as to weaken and then to destroy its reflex function.

Experiment I. A frog was suspended by its lower jaw and the reflex activity tested by dipping the web of both posterior extremities in dilute sulphuric acid (11 min. oil of vitriol to 12 oz. of water). The exact time which elapsed between the contact of the foot and the resulting reflex movement was ascertained by the beats of a métronome, set at one hundred to the minute. Before the administration of the poison the reflex movement occurred in twelve beats. A large dose of extract of Calabar Bean was injected into the abdomen.

In	5	minutes	reflex	movement	occurred	in 15 beats.
...	10	...	...	...	31	...
...	15	...	...	...	40	...
...	20	...	...	...	57	...
...	25	...	...	...	69	...
...	30	...	...	...	82	...
...	35	...	...	...	106	...
...	40	...	...	...	134	...
...	45	...	...	...	165	...
...	50	...	...	...	181	...
...	55	...	...	...	192	...
...	1 hr.	5 m.	no reflex	movement	after	250 ...
...	1 hr.	15 m.	strong acid	caused	no	movement.

The sciatic nerves were then exposed, and weak and carefully localized galvanism applied to either trunk caused energetic contractions of the limb below the portion stimulated, and these contractions could be obtained for two hours after the injection of the poison.

While denying that the asphyxia produced by Physostigma results from any implication of the peripheral motor apparatus, I admit that this poison exerts a special action on these nerves. Motor conductivity is lost more rapidly, in mammals and birds, than after death by agents or means which do not affect these nerves. We can in frogs definitely prove this action if we protect a portion of the animal from the poison by ligaturing the blood-vessels of a limb.

Experiment II. The right iliac artery and the right ischiadic vein were tied in a frog, weighing six hundred and twenty grains, and five grains of alcoholic extract of Physostigma, suspended in thirty minims of distilled water, were injected into the abdominal cavity. In twenty minutes, voluntary movements had completely ceased, there were no respirations, and the frog lay in a perfectly flaccid condition. Fifty minutes after the administration of the poison, the left sciatic nerve was exposed: very weak galvanism of the nerve-trunk caused contractions of the limb, and continued to do so, on occasional observations, till two hours and ten minutes from the commencement of the experiment, or until fifty minutes after the respirations had ceased. It was, however, found to be completely paralysed in other fifteen minutes, or in two hours and twenty-five minutes after the poison was injected. The right sciatic nerve, which had been protected from the influence of the poison by ligature of the blood-vessels of the limb, was examined in a similar manner. *Its motor canductivity continued unimpaired for at least five hours longer than that of the poisoned nerve.*

This is merely an example of numerous experiments which were undertaken for the special purpose of examining this effect of Calabar Bean. From this experiment it can also be shewn that the endorgans of the motor nerves are paralysed before the nerve-trunks. If, after a stimulus, applied to any portion of the nerve of the *poisoned* limb, is followed by no muscular contractions of that limb, we place our electrodes on the nerve of the *non-poisoned* leg above the portion ligatured (that is, where the poison had access to the nerve-trunk), contractions will follow as readily as when these are placed below the ligatures (that is, where the nerve terminations were not poisoned). This result may be confirmed by protecting the endorgans only from the poison, as by ligaturing the vessels of the gastrocnemius, when the muscle supplied by the protected endorgans will alone contract on stimulation of the nerve-trunk.

Dr Harley denies that death ever results from syncope after the administration of this poison. In a former publication I have given details of a most satisfactory description, in which Calabar Bean caused death by its action on the heart[1], and my facts are supported and confirmed by other observers[2]. Until good cause can be shewn to discredit these observations, something further than a mere statement, unaccompanied by proof, is required to support Dr Harley's opinion. It would, therefore, prolong this paper in a very unnecessary manner were I to re-narrate the evidence on this point, or to state the many confirmatory experiments I have since made. It will be sufficient to shew that no connection of cause and effect necessarily exists between the impaired respiratory movements and the cardiac paralysis.

Experiment III. In a large retriever dog it was found that the mean number of respirations was ten, and the mean number of cardiac contractions one hundred and twenty-six, during seven minutes immediately preceding the injection of six grains of extract suspended in water, into the right jugular vein.

1 min.		after the injection				the respirations	= 10,	cardiac contractions	= 78	per min.		
1 ...	30 sec.	...	...	...	...	= 11,	...	...	= 54	...		
2 ...	0 ...	...	...	...	...	= 9,	...	...	= 40	...		
3 ...	0 ...	...	...	...	...	= 9,	...	...	= 8	...		
7 ...	0 ...	...	...	...	...	= 10,	...	...	= 20	...		
9 ...	0 ...	...	...	...	...	= 10,	...	...	= 16	...		
10 ...	0 ...	...	...	...	...	= 9,	...	...	= 9	...		
10 ...	30 ...	...	...	...	...	= 0,	...	...	= 0	...		

This experiment gives the result that, in one minute and thirty seconds after the poison was administered, the cardiac contractions had fallen to less than one half, while the respiratory movements had increased by one per minute, and it distinctly shews the absence of any respiratory change to cause the marked effects which were produced on the heart's action.

Experiment IV. A frog, weighing 460 grains, had its heart exposed by removing the sternum. It was acting at the rate of 48 beats per minute, while the respirations were 72. Five minutes afterwards, the heart was contracting at the rate of 45 per minute, while the respirations were 74. One grain and a half of extract suspended in water was injected by Wood's syringe under the skin of each thigh (three grains in all).

In	5 min.	Heart	= 36	per min.			Respirations	= 74	per min.		
...	10 ...	...	= 28	...			...	= 64	...		
...	15 ...	...	= 22	...			...	= 63	...		
...	20 ...	...	= 14	...	weak, and	...	=	Frequent gasping movements			
...	25 ...	...	= 13	...	continues	...	=	which cannot be counted.			
...	30 ...	...	= 12	...	dark	...	=	An occasional gasp.			
...	40 ...	...	= 10	...	during	...		Respirations have stopped.			
...	50 ...	...	= 10	...	systole.						
...	1 hr. 0 ...	...	= 8	...	very feeble.						
...	1 ... 10 ...	...	= 8	...							
...	1 ... 15 ...	...	= 0	...	stopped in diastole.						
...	1 ... 20 ...	...	= 0	...							
...	1 ... 30 ...	...	= 12	...							
...	1 ... 40 ...	...	= 12	...							
...	1 ... 50 ...	...	= 12	...							
...	2 ... 0 ...	...	= 10	...							
...	2 ... 30 ...	...	= 8	...	irregular: two auricular for one ventricular.						

The heart continued to act in an irregular manner for at least eight hours after the injection, when the observations were stopped.

These experiments prove distinctly that Calabar Bean has a direct influence on the heart, which is quite independent of the indirect influence which it may exert on this organ by arresting the respiratory movements. I think the evidence I have given is sufficient to shew that Dr Harley has

[1] *Op. cit.* Experiments 3, 6, 11, 14, 15, 26.

[2] Christison, *Monthly Medical Journal*, Vol. xx. 1855. Nunneley, *On the Calabar Bean, &c.* 1863, p. 23. Pamphlet. Von W. Laschkewich. Virchow's *Archiv.* Februar. 1866.

to an important extent misinterpreted the phenomena which are produced by Physostigma.

Mr Nunneley, of Leeds, has made an interesting series of experiments with Calabar Bean[1]. He appears to consider that its effects are principally due to a special action on the heart, but he admits that the dose and mode of administration of the poison may so far modify its effects as to cause symptoms of either syncope or asphyxia. I cannot agree with Mr Nunneley in his further statement, that both these results are caused by a common action of Physostigma on the heart and on voluntary muscles. In maintaining that general muscular contractility is lost, Mr Nunneley occupies a position which is contradicted, as far as I know, by every writer on this subject, and his statement is unsupported by any observation which he has published. Far from this being the case, one of the very last symptoms of vitality is the retained idio-muscular contractility. The voluntary muscles always contract long after motor nerve-conductivity has been destroyed, and, in frogs, I have seen distinct muscular action produced by galvanic stimulation five days after the administration of a poisonous dose. In this respect it causes an analogous effect to curare[2], for while in parts separated by ligature muscular contractility is lost within three days, in the poisoned parts it may be retained for two days longer.

Dr Anstie has done me the honour of criticising that portion of my former publication on this subject which refers to the pupil changes produced by the constitutional action of Calabar Bean, in his able and original work on *Stimulants and Narcotics*. As I have already indicated my intention of returning at a future opportunity to this branch of the investigation, I merely, in courtesy to that distinguished observer, wish to refer to one statement which he has made. It is to the effect that Physostigma does not cause contraction of the pupil "when the blood is fully poisoned with it; that it is only the slighter influence, which can alone be produced on iridal movements by local application which causes contraction;" and that "a dose of the bean (taken internally) such as is sufficient to produce acute general poisoning falls with destructive force upon the sympathetic system, producing paralysis of the heart, and dilatation of the pupil[3]." I hope to be able to discuss the theories involved in these assertions on a future occasion, but, as I believe the facts are erroneous, and as they are contradicted in my conclusions, I take this opportunity of stating some of the evidence bearing on them. I find that in twenty-five of my experiments, in which the effects were produced by internal administration, the condition of the pupil was carefully noted, with the results given in the adjoining table.

In many other experiments the pupils are described as having contracted during the poisoning, but the exact changes were not measured. In two or three out of more than a hundred, the pupils are said to have been dilated at the time of the observation. It is possible that this dilatation had not been preceded by a stage of contraction, but I prefer to believe that the examination happened to have been made when the latter had given place to dilatation. In the Table, Experiments 46, 49, 81, 96, 99 and 110 illustrate the occasionally rapid change from contraction to dilatation, and, unless special and continued attention be directed to the condition of the pupils, it is obvious that contraction will frequently escape detection. Harley[4], Amédée Vée[5], Nunneley[6], Laschkewich[7], and van

[1] *Op. cit.* and *Lancet*, 1863.
[2] Claude Bernard, *Leçons sur les effets des Substances Toxiques*. 1857. p. 320.
[3] *Stimulants and Narcotics*. By Francis E. Anstie, M.D. &c. 1864, p. 481.
[4] *Op. cit.* p. 140.
[5] *Recherches sur la Fève du Calabar*. 1865. p. 22, &c.
[6] *Op. cit.* p. 12.
[7] *Op. cit.* p. 300.

TABLE OF PUPIL-CHANGES DURING POISONING BY PHYSOSTIGMA[1].

Experiment.	Animals.	Average before poisoning.	Minimum after poisoning and time of occurrence.	Time of return to average before poisoning.	Dilatation over average and time of occurrence.	
No. 6	Frog	3 × 4[1]	1·75×3 in 46 m.	Not noted	None noted	In 23 m., when the pupil had returned to its average, the animal had nearly recovered from a small dose: the second line marks the effects caused by another and larger dose, given 24 m. after the first.
,, 28	do.	5 × 7	4×5 in 29 m.	4 hrs.	,,	
,, 37	do.	5 × 7	4·5×6 in 16 m.	55 min.	6×7 in 1h.10m.	
,, 38	Rabbit	13 (long. diam.)	4 in 7 m.	Not stated	None noted	
,, 42	do.	9 ,,	4 in 5 m.	15 min.	,,	
,, 43	do.	10 ,,	7 in 11 m.	23 min.	,,	
,, ,,	,,	10 ,,	6 in 7 m.	Not noted	,,	
,, 44	do.	10 ,,	3 in 12 m.	,,	,,	
,, 45	do.	11 ,,	3 in 16 m.	58 min.	,,	
,, 46	do.	9 ,,	3 in 7 m.	8 min.	,,	
,, 47	do.	12 ,,	4 in 8 m.	Not noted	,,	
,, 48	do.	13 ,,	3 in 8 m.	,,	,,	
,, 49	do.	11 ,,	3 in 16 m. 30 s.	17 m. 30 s.	,,	
,, 50	Frog	4 × 6	3·5×5 in 24 s.	Not noted	,,	Eyelids closed, and difficult to see pupil after 24 m.
,, 53	do.	5 × 6	4×5 in 25 s.	2 hrs.	5×6 in 1h.46m.	
,, 73	do.	5 × 6	3×4·5 in 16 s.	2 hrs.	None noted	
,, 76	do.	5 × 6	4×5 in 30 s.	1 hr. 47 min.	,,	
,, 81	Dog	21	17 in 28 m.	29 min.	25 in 30 m.	
,, 82	Frog	5 × 6·5	4×5 in 19 m.	2 hrs. 5 min.	None noted	
,, 83	do.	4 × 5·5	3·5×5 in 11 m.	22 min.	None noted	
,, 85	do.	6 × 7·5	3×5 in 50 m.	Not noted	,,	
,, 96	Dog	21	15 in 4 m.	4 min. 30 sec.	25 in 5 m. 30 s.	
,, 99	do.	10	4 in 5 m. 30 s.	8 min.	15 in 10 m.	
,,110	do.	16	3 in 7 m.	9 min. 30 sec.	None before death	
,,115	Pigeon	6	4 in 8 m.	Not noted	None noted	General symptoms very slowly produced.
,,116	do.	6	4 in 28 m.	Not noted	,,	

Hasselt[2] agree in describing contraction of the pupils as one of the effects which follow the internal administration of Calabar Bean.

Dr Laschkewich of St Petersburgh has recently published an elaborate investigation, and has, in a most satisfactory manner, confirmed my results. The conclusions which this physiologist has arrived at are:—1. Calabar Bean affects the spinal cord, and so produces a general paralysis. 2. It also paralyses the heart. 3. Division of the nervi vagi does not prevent the heart from being influenced. 4. Calabar Bean causes contraction of the pupils either by topical application or by action through the blood. 5. It increases the flow of saliva and of tears. 6. The sympathetic nerves and intestinal muscles are paralysed by Calabar Bean. 7. The peripheral nerves, the muscles of the body, and the brain are not affected. 8. When the poison was put directly into the blood, death followed by cardiac paralysis; but when it was injected under the skin (i.e. by slow poisoning) death was caused by asphyxia.

The sixth and seventh of these conclusions are not strictly in accordance with my results. On the former, I must refer to the 14th and 19th of the general conclusions at the end of this paper; and, on this point, I have the support of so trustworthy an observer as Professor Donders[3]. Dr Laschkewich has evidently overlooked the paralysis of the motor endorgans by restricting his examination to the question of how far the motor nerves are concerned in the production of the general paralysis. Finding that

[1] The figures represent fiftieths of an inch: the measurements were made with a glass scale each division of which equalled the one fiftieth of an inch.

[2] Quoted by Donders (Accommodation and Refraction of the Eye: New Sydenham Soc. 1864) as having been observed in 1856, and, I am informed by Prof. Donders, communicated to a scientific society, but not otherwise published by van Hasselt.

[3] Accommodation and Refraction of the Eye: New Sydenham Society, p. 616.

the peripheral motor apparatus was unaffected when the respiratory movements had ceased, he appears to have considered the question as decided; whereas, a further examination, especially by limitation of the poisoning, would have given unmistakeable evidence of the action of Physostigma on the terminations of the motor nerves.

In the investigation, of which the conclusions will now be given[1], an extract, prepared by acting on the finely pulverized kernel with boiling alcohol (85 p. c.), has been used. This preparation contains a considerable proportion of fatty matter, which prevents its perfect solution in water; and, as the division into separate doses of a mere watery suspension would lead to many inaccuracies, it was found necessary to weigh the requisite quantity separately for each experiment. This extract is hygroscopic, which further required that it should be dried and kept in an exsiccator. The majority of the experiments were made with the common frog (Rana temporaria), birds, and various mammals. It was found that fatal results were produced with the smallest quantity on birds, and that the largest doses, in proportion to weight, were required by amphibia. A dose of one-sixteenth of a grain proved rapidly fatal to a pigeon, whereas three grains have been recovered from by a frog—a quantity sufficient to produce death in a dog of average size.

The following are the conclusions of my investigation.

A. *Action through the Blood.*

1. Physostigma proved fatal to every animal hitherto examined, with the exception of the Eséré moth[2]. Death is most rapidly caused, in birds and mammals, by the injection of the poison into the circulation, or when it is brought in contact with a wounded surface. It follows, nearly as quickly, when Calabar Bean is introduced into a serous cavity, and, much less rapidly, when introduced by the mucous membrane of the digestive system. In rabbits, death has been caused by its application to the Schneiderian, auditory, and conjunctival mucous membranes. The skin of frogs resists its effects for a long time; but, if applied for a sufficient period and with proper precautions, distinct evidence of its absorption may be obtained, though death has never been caused by such application.

2. The contact of the extract of Calabar Bean with the gastric juice of a dog for twenty-four hours, at a temperature a little above 95° F., did not, in the slightest degree, modify its energy.

3. A large dose, given to a mammal or bird, rapidly affects the cardiac contractions, and then paralyses the heart. The respiratory movements are quickly stopped, but the symptoms and *post-mortem* appearances are those of syncope. Such a dose, injected into the abdominal cavity of a frog, affects nearly simultaneously the heart and spinal cord[3], and very rapidly destroys the vitality of both organs. With such a dose the motor nerves are unaffected, and retain their conductivity for at least thirty hours. Evidence of the vitality of the afferent nerves may be obtained so long as the retained vitality of the spinal cord permits of its diastaltic function being examined.

4. An average dose produces symptoms of asphyxia in mammals and birds. When administered to frogs, a similar dose impairs the function of the spinal cord, and diminishes the rate of the cardiac contractions and of the respiratory movements, and, soon after, the latter cease. In periods,

[1] The investigation, from which these results are derived, has been laid before the Royal Society of Edinburgh, and an abstract is published in the Society's *Proceedings* for 1867.

[2] *The Annals and Magazine of Natural History*. Vol. xiii. 1864. p. 389.

[3] The effects on the spinal cord were determined by frequent measurements of the reflex activity by means of a métronome.

varying from one and a half to four hours afterwards, the motor nerves are paralysed; this paralysis first implicating the endorgans of these nerves, and afterwards the nerve-trunks. From this it must not be inferred that the nerve is paralysed by a centripetal progression of the poison, the only fact which was demonstrated being that a direct ratio existed between subdivision of nerve substance and facility of contact of poison, on the one hand, and, on the other, rapidity of paralysing effect. Indeed, division of the nerve-trunk, previous to the administration of Calabar Bean, delayed the paralysis of its endorgans. The afferent nerves retain their activity so long, at least, as the functions of the spinal cord are not lost, and this generally happens about the same time as the motor paralysis.

5. When a small, but still fatal, dose of Calabar Bean is administered to a frog, the effects are the same as those in the previous conclusion, until they arrive at the stage of paralysis of the motor nerves, and, after this, an interval of several hours may elapse before the functions of the spinal cord are completely suspended. During this interval the *tactile* sensibility of the afferent nerves is increased; so that, if the ischiadic artery and vein of one limb were tied before the exhibition of the poison, an ordinary excitant, such as sulphuric acid, will show everywhere a marked diminution in the diastaltic activity, as measured by the métronome; while a slight touch of the skin in the poisoned region, which before the administration of the poison caused no effect, will now produce faint twitches of the limb whose vessels are tied.

6. *A frog may have its cardiac contractions reduced from seventy to eight per minute, its respiratory movements completely stopped, and the endorgans of its motor nerves paralysed, by a still smaller dose, and afterwards completely recover.* This has occurred when two grains were injected into the abdominal cavity of a frog, weighing seven hundred and thirty grains.

7. In frogs the voluntary muscles are unaffected by the poison, and may continue to respond to galvanic stimulation during three or four days after its administration. The contrast and independence in the effects of Calabar Bean on the motor nerves and on the muscles may be well shewn by ligaturing the ischiadic vessels of one limb before injecting the poison. If, when strong stimulation causes no reflex movement, the two gastrocnemii muscles with their attached nerves are so placed that an interrupted current, from one Daniell's cell and Du Bois Reymond's induction apparatus, may be transmitted simultaneously, either through both muscles or both nerve-trunks, it will be found, in the case of the muscles, that when the secondary coil is slowly advanced contractions will occur with the same current in both muscles, or with a weaker current in the case of the poisoned than of the non-poisoned muscle, this varying with the length of time which has elapsed since the limb was deprived of blood; when the current is transmitted through both nerves, contractions will be simultaneously produced, or with a weaker current in the non-poisoned, or contractions will occur in the non-poisoned muscles only, this also varying with the length of time which may have elapsed since the exhibition of the poison.

8. In mammals and in birds the voluntary muscles are affected in a very remarkable manner. At an early stage of the poisoning, faint twitches occur, which gradually extend over the body, and, at the same time, increase in vigour so as to interfere with the respiratory movements. Shortly before death they again become mere successive twitches, often requiring the hand to be placed over the part to discover their existence. After death, if a muscular surface be exposed, these twitches will still be observed, rarely involving the whole of one muscle, but at different times different muscular fasciculi; and in mammals they may persist for more

than thirty minutes after death. They are caused by a direct effect of Physostigma on the muscular substance. This is shewn by their continuing after paralysis of the motor nerves, by their persisting in a muscle cut out of the body, and by their non-occurrence in parts which have been separated by ligature from the circulation.

9. The heart's action is rapidly made slower and then stopped, in birds and mammals, by a large dose. In dogs it may diminish to one-half in three minutes, and cease in ten. A large dose injected into the abdominal cavity of a frog causes rapid and complete cardiac paralysis. A smaller dose causes either a gradual cessation and then a renewal at a diminished rate, or a gradual fall from sixty or seventy to four or six beats per minute, followed by a gradual return to a diminished rate of eight or twenty per minute. At this stage, and for many hours afterwards, the only signs of vitality are this diminished cardiac action and the power of the voluntary muscles to respond to galvanic and other stimulation. In the frog, where alone these last phenomena have been observed, the heart may continue so to contract for three, and for even five, days, provided the temperature of the apartment be as low as 50° F. After stoppage, galvanism may cause a renewal of its rhythmical contractions; but this can rarely be done, and unrhythmical and partial contractions can only be excited. The heart ceases to contract in diastole, with all its chambers full.

10. The pneumogastric nerves retain their inhibitory power over the heart during the whole time from the diminution to the partial recovery of its action. Soon after this, however, they are paralysed: and this occurs at nearly the same time as the affection of the motor nerves.

11. Division of the pneumogastric nerves, or their previous paralysis by curare, or destruction of the medulla oblongata or spinalis, does not protect the heart from the action of Physostigma.

12. The lymphatic hearts of frogs poisoned by Calabar Bean soon cease to contract.

13. A large dose paralyses the cervical sympathetic nerves, in rabbits, before the death of the animal. A smaller fatal dose diminishes, without destroying, their activity.

14. Before the stoppage of the heart, proofs may be obtained of the vitality of its sympathetic ganglia; but, as striped muscle is not affected by Calabar Bean conveyed by the blood, we are obliged to infer, from the symptoms respectively produced, that the activity of the cardiac sympathetic system may be destroyed by a large dose, and lessened by a smaller one.

15. The animal temperature, both external and internal, has been invariably observed to rise in rabbits and dogs, but only slightly.

16. The condition of the capillary circulation was examined in the web of the frog. Soon after the exhibition of the poison the smaller arteries and veins contracted slightly; after a short interval, this contraction was succeeded by a rapid and permanent dilatation, in which the calibre of the vessels was considerably above their maximum previous to the poisoning. This capillary dilatation appears to occur over all the body, as is shewn by a peculiar blue coloration of the voluntary muscles and of the heart, a similar coloration of the serous and fibro-serous tissues, and a congestion of the blood-vessels in the conjunctiva and iris. This change also occurs, in a less marked manner, in birds and mammals.

17. The general results of experiments in which the arterial and venous tensions were examined were, that almost immediately after the administration of Calabar Bean the arterial tension rose slightly, attained its maximum when the number of cardiac contractions had diminished to at least one half, and, then, rapidly fell; and that the venous tension rose

less quickly, attained its maximum when the arterial tension had considerably diminished, and, in its turn, fell, though more gradually than that of the arterial system. The number of the cardiac contractions, when the venous tension had attained its maximum, was about one-third of the average before the poisoning; the respirations were rather less frequent than before; and the temperature had risen a few tenths of a degree.

18. Physostigma causes extreme diffusion in the pigment cells of the frog's skin, and, so, a very marked change occurs in the colour of the animal during the progress of the symptoms.

19. In dogs, the peristaltic action of the intestines is usually destroyed at death; it may, however, continue a short time afterwards. In rabbits, the intestinal movements are frequently increased in activity before death, and they generally continue for a considerable time afterwards.

20. The pupil contracts in all cases of rapid poisoning in mammalia and in birds. The contraction may, however, be slight and of short duration, and dilatation may then be observed during the greater portion of the experiment, especially if the dose be a small one. The same effect is produced in frogs.

21. Calabar Bean acts as an excitant of the secretory system, increasing the action of the alimentary mucous, of the lachrymal, and of the salivary glands.

22. The symptoms of poisoning are not materially altered, in the frog, by removal of the brain, or by division of the cervical portion of the spinal cord.

23. Artificial respiration does not prevent death, in mammals, after the exhibition of a poisonous dose. This is a necessary result of the effects of Physostigma on both the cerebro-spinal and sympathetic systems.

24. Congestion of internal organs occasionally occurs, but this is by no means an invariable consequence of a fatal dose.

25. The blood is dark after death, but becomes arterialized on exposure to the air; its respiratory functions are unaltered; it often clots loosely and imperfectly; and, when examined with the spectroscope, the bands of scarlet crurine are found unchanged. A microscopic examination demonstrates, in the rabbit and dog, an invariable change in the coloured corpuscles which have their outlines distinctly crenated. This change is not observed in the blood of birds or of amphibia. The white corpuscles remain unaltered.

B. *Topical Effects.*

1. When applied to the surface of a frog's brain no effect is produced; but when the poison is brought in contact with the spinal cord, a few twitches occur in the extremities, followed by paralysis of the portion of cord acted upon.

2. When physostigma is applied to a mixed nerve-trunk, in a concentrated form and with proper precautions to prevent absorption, the afferent nerve-fibres are first paralysed, and, afterwards, the efferent.

3. Topical application destroys the contractility of striped and of unstriped muscular fibre. The heart's action is stopped by repeated application to its external surface or to the pericardium. If a small quantity be injected into one of its chambers, paralysis nearly immediately follows.

4. The effects of the application of Calabar Bean to the eye-ball are a somewhat painful sensation of tension in the ciliary region, contraction of the pupil, myopia and astigmatism, congestion of the conjunctival vessels, pain in the supra-orbital region, and twitches of the orbicularis palpebrarum muscle.

Many of these physiological results indicate therapeutical properties of great value, and several of these have been already pointed out in my first

paper on this subject[1]. The unmistakeable success which has followed the recommendation that was there made to employ Physostigma in the treatment of tetanus, first, under M. Giraldès, of Paris, and, very recently, in the hands of Dr E. Watson, of Glasgow[2], encourages me to hope that this substance will prove even more valuable to the physician than to the ophthalmic surgeon.

OBSERVATIONS ON BRITISH ZOOPHYTES AND PROTOZOA.

By T. Strethill Wright, M.D., &c.

(*Plates* XIV. and XV.).

1. *On Stomobrachium octocostatum* (Forbes).

Stomobrachium octocostatum (Forbes) is occasionally found in the Firth of Forth, in the neighbourhood of Queensferry, and Granton. All the specimens of this animal which I have taken have been females, and as Stomobrachium is one of those medusæ which feed and thrive well in captivity, I have repeatedly endeavoured to obtain young zoophytes from it in the hydroid stage of their existence, but hitherto without success, as the development of the ova in the ovarian bands invariably became arrested soon after the animals were removed from the sea. I have little doubt, however, that the hydroid phase of Stomobrachium will eventually be obtained, and that it will be a Tubularian polyp, allied to Atrachylis or Clavula, inasmuch as its medusoid form is destitute of otolithic sacs, organs which have hitherto been found always absent in the medusoids of Tubularian zoophytes. Several years ago I accidentally noticed such a hydroid, as a single, minute, yellowish polyp, resembling Clavula, and having three rows of filiform tentacles, attached to a stone in a large tank, in which a specimen of Stomobrachium was confined with some other zoophytes, but I was not able to establish any connection between the polyp and the medusa, as the planuloid larvæ of the latter were not ripe for extrusion, and never became so, although the medusoid lived for several weeks.

On examining a specimen of Stomobrachium last summer, which had been recently fed on the whiter parts of an oyster, I noticed a retiform system of fine canals, Fig. 1 *a*, *a*, *a*, permeating the muscular web of the sub-umbrella and altogether distinct from the eight large lateral canals which carried the ovarian bands. This new canal system consisted of from three to five fine tubes, which sprung from the upper margin of the peduncle, between each of the lateral canals, and passed outwards and downwards as a rarely anastomosing network, to join the circular canal bordering the mouth of the umbrella. No branches from it communicated with the lateral canals, nor could they do so as the latter were bordered on each side by the long ovarian bands.

Throughout the whole supplementary system the presence of ciliary action was indicated by the vibratory and onward movement of the milky fluid contained therein, and it is evident that the function of this system is to supply nutrient material to the powerful muscular tissue of this rapidly swimming medusa.

As far as I know, no similar canals have been detected in any of the Gymnopthalmatous medusa. In Willsia the peripheral extremity of the lateral canals is branched, but this must not be confounded with the separate system I have described above.

[1] *Op. cit.* Sect. iv. [2] *Lancet*, March 2, 1867.